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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,974	10/26/2001	Gabriel Nunez	UM-06646	3481

7590 03/13/2003

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/13/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,974	NUNEZ ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,12,24-31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,24-31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed January 13, 2003. Currently, claims 1-9, 11-12, 24-31, 33 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group I in Paper No. 8 is acknowledged.

It is noted that applicant's did not elect a single sequence or single SNP within the scope of the claims for prosecution. In the event that applicant's amend the claims, the examiner reserves the right to impose the restriction upon any newly presented claims.

Priority

3. This application claims priority to provisional applications 60/244,266, filed October 30, 2000 and 60/286,316, filed April 25, 2001.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). In the first line of the instant specification, the claim fails to provide the date in which the provisional applications were filed.

It is noted that the provisional filed in October 30, 2000 only appears to teach a single variation within the scope of the claims, namely an insertion of C which results in the truncation of the protein.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9, 11-12, 24-31, 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of identifying subjects at risk of developing Crohn's disease by detecting the presence or absence of one or more variations in a Nod2 gene.

The specification teaches specific examples which have sequenced a Nod2 gene on chromosome 16q12. The genomic organization of the Nod2 gene was 12-exons (page 118). The specification teaches amplifying all coding exons and flanking introns in DNA samples from CD individuals (page 118, lines 25-32). A cytosine insertion was observed in exon 11 at nt 3020 (page 118, lines 30-31). The insertion resulted in a frameshift at the second nucleotide of codon 1007. Figure 26 illustrates 7 additional polymorphisms that were identified in Nod2 gene (page 124). The specification teaches

a significant association between Nod2 33, G908R, and R702W with Crohn's disease (page 125-126). As seen in Table 3, each of the p-values for these polymorphisms is less than 0.05.

Moreover the post filing date art establishes that the Nod2 gene was discovered by three independent groups. In addition to the publication by Ogura et al (Nature, Vol. 411, pages 60-3606, May 2001), Hampe et al (The Lancet, Vol. 357, pages 1925-1928, June 16, 2001) and Hugot et al. (Nature, Vol. 411, pages 599-603, May 2001) teach mutations in Nod2 and Crohn's disease association.

Hampe et al. (herein referred to as Hampe) teaches screening for mutation in Nod2 by genomic resequencing or denaturing high-performance liquid chromatography. The analysis yielded 12 mutations including a C-insertion mutation in exon 11. Hampe teaches that the C insertion mutation was significantly significant at a p-value of <0.0001.

Hugot et al. (herein referred to as Hugot) teaches the identification of Nod2 mapped to chromosome 16. In Figure 1, multiple SNPs are identified pictorially in the Nod2 gene. Moreover, Table 1 provides each of the SNPs, their location and the association studies with Crohn's disease. When comparing the table to the SNPs identified in the instant application, it appears as though four of the mutations are in common. For example, SNP5 of Hugot appears to correspond to SNP4 of the instant application.

	Hugot Table	Significance in Hugot	Instant Application	Significance in instant application
P268S/P214S	SNP5	0.0001	SNP4	Not determined
R675W/R702W	SNP8	0.001	SNP20	0.0010
G1881R/G908R	SNP12	0.003	SNP17	0.00010
2936insC/ Nod2 33	SNP13	0.000006	C ins	0.0018

Of the additional SNPs provide by Hugot, four of the 13 are not significant. The instant specification is silent with respect to the significance of any of the additional SNPs within the instant application.

The French document of Hugot also provides additional variant nucleotides within the Nod2 gene. There appear to be approximately 24 variations taught within Table 3 on page 36-37. The table provides the exons within the Nod2 gene in which each of the markers occurs, the position of the variant nucleotide, the position in the variant protein, the frequency in individuals with Crohn's disease, and finally in the last column, the presence of the mutation in normal individuals.

There is not adequate description of the genus of variations within the scope of the claims. The specification has only taught seven single nucleotide polymorphisms and one insert polymorphism within the Nod2 gene. Variations is a very broad term

which has not been explicitly defined in the specification. Variations within nucleotide sequences encompass not only single nucleotide polymorphisms and insertions, but also mutations, translocations, microsatellite markers, trinucleotide repeat regions, etc. The description of 8 of these variations is not a representative number. Therefore, the description of these 8 markers are not representative of the genus as a whole. Based upon the post filing date art, at the time the invention was made, a representative number of marker within the scope of the claim was not disclosed. It is clear that the specification had not described the 11 additional markers taught by Hugot. Moreover, in the French document by Hugot, additional markers have been taught which were not disclosed in the instant application. There is substantial variability among the species of nucleic acids encompassed in the scope of the claim because only two specific mutations have been identified in the gene with 12 exons. The specification has also not defined a structural feature of the variations which would be common to all members of the genus that constitutes a substantial portion of the genus. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "variation in the Nod2 gene" because the description of only eight members of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the specification does not adequately provide a written description for variants in Nod2.

Moreover, with respect to "variations which result in increased NF-B activation," "cytosine residue insertion," "mutation which causes a deletion of a least one LRR repeat of Nod2" (Claims 7-9) the specification has described a single mutation

within the scope of the claims. The specification has not described a representative number of mutations which insert a cytosine residue, increase NF-B activation or cause a deletion of at least one LRR repeat of Nod2.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9, 11-12, 24-31, 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of identifying subjects at risk of developing Crohn's disease by detecting the presence or absence of one or more variations in a Nod2 gene.

The specification teaches specific examples which have sequenced a Nod2 gene on chromosome 16q12. The genomic organization of the Nod2 gene was 12-exons (page 118). The specification teaches amplifying all coding exons and flanking introns in DNA samples from CD individuals (page 118, lines 25-32). A cytosine insertion was observed in exon 11 at nt 3020 (page 118, lines 30-31). The insertion resulted in a frameshift at the second nucleotide of codon 1007. Figure 26 illustrates 7 additional polymorphisms that were identified in Nod2 gene (page 124). The specification teaches a significant association between Nod2 33, G908R, and R702W with Crohn's disease (page 125-126). As seen in Table 3, each of the p-values for these polymorphisms is less than 0.05.

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Nod2 gene. Moreover, Table 1 provides each of the SNPs, their location and the association studies with Crohn's disease. When comparing the table to the SNPs identified in the instant application, it appears as though four of the mutations are in common. For example, SNP5 of Hugot appears to correspond to SNP4 of the instant application.

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Of the additional SNPs provide by Hugot, four of the 13 are not significant. The instant specification is silent with respect to the significance of any of the additional SNPs within the instant application.

The French document of Hugot also provides additional variant nucleotides within the Nod2 gene. There appear to be approximately 24 variations taught within Table 3 on page 36-37. The table provides the exons within the Nod2 gene in which each of the markers occurs, the position of the variant nucleotide, the position in the

variant protein, the frequency in individuals with Crohn's disease, and finally in the last column, the presence of the mutation in normal individuals.

Neither the art nor the specification enable the skilled artisan to make and use the claimed invention as broadly as claimed. First, the specification asserts that the instant invention discovered the Nod2 gene. It is not well known in the art the scope of Nod2 gene. Therefore, aside from the few Nod2 genes discussed in the specification by SEQ ID NO:, the ordinary artisan would be unable to ascertain what constitutes a Nod2 gene. The Nod2 gene does not have any functional activitiy, in which the ordinary artisan would be able to assay for to reasonably confirm that the nucleic acid examined is in fact a Nod2 gene. Thus, absent some structural information, the skilled artisan would be unable to identify a gene by the arbitrary gene name Nod2.

Moreover, the teachings in the specification do not establish that one could actually detect the presence of any variation in the Nod2 gene as an indicator of developing Crohn's disease. Rather the teachings in the specification demonstrate that the presence of three specific variations within the gene are associated with an increase risk of Crohn's disease. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the prior art also provides numerous variations within the scope of the claims which have been demonstrated not to have an association with Crohn's disease. As seen in Hugot, approximately four of the markers studied failed to have any association with Crohn's disease. Moreover, in Hugot's foreign document, Table 3 illustrates that several of the mutations are found more frequently in normal individuals than in Crohn's

patients or that the variation is found in neither of the populations. Thus, it is unpredictable as to whether one could successfully use the full scope of the claimed invention. While one could conduct additional experimentation to find additional variations within the Nod2 gene and to determine whether an association exists between the newly discovered variation and Crohn's disease, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. Claims 2-4 appear to be directed solely to research projects to determine whether unknown and undescribed variations with in the Nod2 gene are associated with Crohn's disease. The ordinary artisan would uses the steps to perform the additional experimentation that is deemed necessary to perform the entire scope of these claims.

The method relies on detecting the presence or absence of mutations to identify subjects at risk of developing Crohn's disease. The absence of a mutation in Nod2 has not been demonstrated to be indicative of a lack of Crohn's disease. The art teaches (Hugot- French document) that the mutations are present in normal individuals, but there is a significant difference between the presence of the mutation in Crohn's disease patients and normal individuals. Therefore, the claims would be more properly drawn to detecting the presence of the variation as indicative of Crohn's disease.

Moreover, with respect to "variations which result in increased NF-B activation," "cytosine residue insertion," "mutation which causes a deletion of a least one LRR repeat of Nod2" (Claims 7-9) the specification has taught a single mutation within the scope of the claims. The skilled artisan would be required to perform undue and

unpredictable experimentation to determine whether any additional variations within the scope of the claims insert a cytosine residue, increase NF-B activation or cause a deletion of at least one LRR repeat of Nod2.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9, 11-12, 24-31, 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-9, 11-12 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for identifying subjects at risk for developing Crohn's disease but the final process step is detecting the presence or absence of one or more variations. Therefore the claims are unclear as to whether the method is a method of identifying subjects at risk for developing Crohn's disease or merely detecting the presence or absence of one or more variations. This rejection may be easily over come by amending the claim to recite, "wherein the presence of an insert of a cytosine at position 3020 of SEQ ID NO: 1 is indicative of an increased risk of Crohn's disease."

B) Claims 1-9, 11-12, 24-31, 33 are indefinite because the designation Nod2 is arbitrary. The instantly disclosed polypeptide could be identified by some other arbitrary name, or the name Nod2 could be arbitrarily used to designate another polypeptide.

This rejection may be overcome by providing descriptive characterization of the claimed polypeptide.

C) Claims 24-31, 33 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for determining a patient's risk for developing Crohn's disease but the final process step is calculating said patient's risk with said software. It is unclear based upon the final process step how one could determine the patient's risk by merely have a computer calculate the risk. The risk would need to be displayed and available for interpretation. This rejection may be easily over come by amending the claim to recite, "displaying said patient's risk wherein the presence of an insert of a cytosine at position 3020 of SEQ ID NO: 1 is indicative of an increased risk of Crohn's disease."

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
March 10, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600